



⑯ Europäisches Patentamt
European Patent Office
Office européen des brevets

⑮ Publication number:

0 263 083
A1

⑯

EUROPEAN PATENT APPLICATION

㉑ Application number: 87830347.8

㉓ Int. Cl.⁴: A 61 K 9/52
A 61 K 9/42

㉒ Date of filing: 29.09.87

㉔ Priority: 30.09.86 IT 353086

㉕ Applicant: Valducci, Roberto
Via del Sole, 4
I-47039 Savignano sul Rubicone (Forlì) (IT)

㉖ Date of publication of application:
06.04.88 Bulletin 88/14

㉗ Inventor: Valducci, Roberto
Via del Sole, 4
I-47039 Savignano sul Rubicone (Forlì) (IT)

㉘ Designated Contracting States:
AT BE CH DE ES FR GB GR LI LU NL SE

㉙ Representative: Pederzini, Paolo
BUGNION S.p.A. Via Farini n. 37
I-40124 Bologna (IT)

㉚ Coating membrane and compositions prepared therefrom.

㉛ A coating membrane for pharmaceutical, veterinary, cosmetic, synthetic and extractive compounds is provided, which comprises a lipophilic substance alone or in admixture with a hardening agent, wherein the lipophilic substance is selected from fatty acids of from 12 to 20 carbon atoms and paraffin, and the hardener is selected from cellulose ethers or esters, methacrylic acid copolymers, polyethylene glycol, polyvinylpyrrolidone, polyvinylacetophthalate and polyvinylacetate.

EP 0 263 083 A1

Description**"Coating Membrane and Compositions Prepared therefrom"**

This invention relates to a coating membrane for pharmaceutical and industrial purposes and to compositions prepared therefrom. More particularly it relates to a coating membrane for the controlled release of an active ingredient which may be of pharmaceutical, veterinary, synthetic or extractive type, and to compositions containing said coated active ingredient.

In the pharmaceutical field, the production of sustained release microgranules is known (see for example EP 123,470 and 122,077).

The preparation involves the application of the active ingredient on a spherical nucleus having a diameter of from 0.2 to 2 mm by means of a particular binding agent, or a spherical nucleus of active ingredient with or without binding agent may be prepared. Then a semi-permeable membrane is applied, which allows the diffusion of the drug over a controlled period of time or it disintegrates over a well-established period of time releasing the drug.

The membrane normally used and described in several patents consists of: shellac, methacrylic acid copolymers, ethylcellulose, ethylcellulose phthalate, hydroxypropyl methylcellulose, cellulose acetophthalate, etc. The abovementioned and currently used membranes are also of natural source, such as shellac, and thus of indefinite composition. As a consequence, the amounts used to obtain an identical coating notably change from time to time and give, therefore, stability problems. The productions from batch to batch are thus difficult, and often it is not possible to obtain the same release pattern.

Moreover, it is very difficult to reach a zero order release or a release over a controlled period of time according to the drug needs.

In the pharmaceutical field, the purpose of the sustained release formulations is to obtain a 12 hours therapeutically active hematic level with consequent posology of two daily administrations, or else a 24 hours hematic level with administration of a sole capsule a day. In order to achieve said results, the drug release has to be more or less delayed according to the characteristics half-life of each drug.

It has now been found that, modifying the amount of the applied membrane or the ratios between two components, it is possible to obtain sustained releases from 4-6 hours up to 18-22 hours and higher, as shown in figure 1 for ketoprofen (ethylcellulose/stearic acid membrane) and in figure 2 for diltiazem hydrochloride (paraffin/methacrylic acid copolymers membrane).

This technological flexibility allows to choose the most suitable in vitro release for obtaining the in vivo blood level which provides the pharmaceutical effect over a desired period of time.

Several tests have shown a very good reproducibility from batch to batch and good stability. Membranes from synthetic products with a well-defined molecular composition, and often reported in International Pharmacopeias, provide an improved

purity, as shown by the analytical tests.

These new membranes, like paraffin, have for their own nature a very low chemical affinity for the products which have to be coated. In this way, a very good compatibility does exist between membrane and product to be coated, and a good time stability may be achieved.

Accordingly, the present invention relates to the use, as semipermeable or breakable membranes, of lipophilic compounds alone or in admixture with a suitable hardening agent. More particularly the present invention relates to a coating membrane for pharmaceutical, cosmetic, veterinary, synthetic and extractive substances and to the compositions prepared therefrom.

In a further embodiment, the invention provides also a method for preparing said compositions, which comprises coating inert material pellets with a first layer of a therapeutically active compound and applying then thereon a second layer consisting of a lipophilic substance, alone or in admixture with a hardening agent.

In the compositions of the present invention, the inert pellets comprise preferably sucrose and starch.

The substances used as lipophilic membranes are the following:

A) Fatty acids containing from 12 to 20 carbon atoms, such as palmitic acid, and/or paraffin (USP XXI, page 1584).

The compounds utilized for having hardening action are selected from :

B) Ethylcellulose Hercules with Ethoxy groups 44.5 to 50%.

C) Hydroxypropylmethylcellulose (Dow Chemicals type E Premium, viscosity form 50 to 4000 cps).

D) Hydroxyethylcellulose (Hercules Natrosol, viscosity from 180 to 250 cps).

E) Hydroxypropylcellulose (Hercules, Klucel, viscosity from 150 to 6500 cps).

F) Hydroxypropylmethylcellulosephthalate (Shinetsu Chemicals, Tokyo).

G) Methylcellulose (Dow Chemical-Methocel Premium; viscosity from 15 to 4000 cps Henkel, Viscontran).

H) Methacrylic acid copolymers (Rohm Pharma GmbH) Eudragit E, L, S, RS, RL, E 30D, L 30D, RL 30D, RS 30D type.

I) Cellulose Acetophthalate (Kodak).

L) Polyethyleneglycol (Hoechst PEG, molecular weight from 300 to 35000).

M) Polyvinylacetate (PVA) (Colorcon UK) (Canada Packers Chemicals, Canada).

N) Polyvinylpyrrolidone (PVP) (BASF, Kollidon, k values from 10 to 95).

O) Hydroxybutylcellulose (Dow Chemicals, viscosity 12000 cps).

P) Carboxymethylcellulose sodium (Henkel Dehydazol, viscosity 400-15000 cps).

Q) Polyvinylacetophthalate (PVAP) (colorcon,

UK) (Canada Packers Chemicals, Canada).

All the hardening agents mentioned above are preferably dissolved in ethanol, acetone, methylene chloride or in other organic solvents at room temperature or at a temperature corresponding to the boiling point of the employed solvent. In this way, 0.1% to saturated solutions may be obtained. The hardeners can be dissolved alone or mixed each other in all the proportions.

The lipophilic substances are dissolved in the above solvents or they are melted. They can be used alone or in admixture each other, and they are applied melted or in solution.

Tests carried out on theophylline with stearic acid alone as membrane, show a faster release in comparison with that obtained with the same amount of stearic acid but added with hydroxypropylmethylcellulose. Adding hardening agents to the lipophilic compounds, a more flexible and less rapid release over a controlled period of time may be achieved. In order to obtain mechanically harder and more stable membranes, the lipophilic compounds should be blended with the hardening agents in solution, where possible, or in alternate layers.

In this case, the preferred ratio lipophilic compound to hardening agent is of from 0.1 to 100% for the lipophilic substance and of from 0.9 to 99.9% for the hardener. The application of the membranes on microgranules or other material which has to be coated, is done for achieving: a slow release of the coated material, gastroprotection, separation of incompatible substances, reduction of the chemical reactivity, physical separation, handling improvement, to eliminate bad smell and taste, stability improvement. The melted or solubilized membrane is applied on the material which has to be coated by means of high pressure pump in order to subdivide it in microdrops.

Said procedure is carried out in stainless steel coating pans with variable rotation speed from 3 to 40 rpm according to the diameter, with a fluid bed apparatus (uni-glatt) or in fast mixers, such as Loedige type or the like. The evaporation of the solvents utilized in the process, is performed in thermostatic dryers or under vacuum at a temperature of from 30° to 45°C.

The lipophilic compounds, alone or mixed each other, and with possible addition of hardening agents, can also be used with spray dry or spray cooling techniques.

The following examples illustrate the invention and facilitate its understanding.

Example 1

On 19 kg of neutral pellets, consisting of 75% w/w of sucrose and 25% (w/w) of starch and placed in a stainless steel coating pan, ketoprofen was applied (53.5 kg) with a 20% (w/w) alcoholic solution (ethanol) of polyethylene glycol (MW 4000). After drying, a 4.5% (w/w) alcoholic solution of ethylcellulose (with 44.5 to 50% of ethoxy groups) and 7.5% of stearic acid was applied, with addition of 2.70 kg of talc.

After drying, the product contained 2.23 kg of stearic acid (NF XVI, page 1611) and 1.33 kg of

ethylcellulose. The release test, carried out according to USP XXI, Apparatus No. 1, at 150 rpm and with 900 ml of juice of pH 7.2, provided the results reported in figure 1, curve D. The curves A to C were obtained with formulations having increased amounts of membrane. With said formulation, capsules containing from 50 to 250 mg of ketoprofen may be prepared.

Example 2

82.00 kg of paracetamol were placed in a Loedige type mixer, and under stirring 12.40 kg of stearic acid (NF XVI, page 1611), melted and blended with 25.00 kg of a 10% (w/w) ethanolic solution of ethylcellulose (44.5-50% ethoxy groups), were added at a temperature of 50-60°C.

The mass was stirred for 10-15 minutes and then dried in a thermostatic box at 35-45°C. The granulate thus obtained had a masked taste and can be used in monodose bags or in other pharmaceutical forms. The granulate was mixed with 3.00 kg of magnesium stearate and tablets containing from 200 mg to 1 g of paracetamol were then prepared.

The release test, accomplished according to USP XXI, Apparatus No. 2, at 50 rpm and with 900 ml of juice of pH 5.8, showed the following release results:

1st hour = 22.8%
4th hour = 54.6%
8th hour = 98.3%

The release rate was increased or decreased by proportionally varying the amount of the applied membrane.

It should be noted that instead of a Loedige type mixer, a fluid bed or stainless steel coating pan may be used and with the same membrane comparative results may be obtained.

Example 3

Operating as described in Example 2, but applying only the 10% of membrane, tablets were obtained showing a very rapid release. With a further coating of the tablets in the stainless steel pan using from 10 to 20% of the same membrane, the following release profile was obtained:

1st hour = 10-25%
4th hour = 40-80%
8th hour = 70-100%

Example 4

Operating as described in Example 1, on 34.40 kg of inert granules (size 0.7 - 1 mm) 49.50 kg of propanolol HCl were applied with 11.00 kg of a 20% (w/w) ethanolic solution of polyvinylpyrrolidone (k value = 30).

The membranes were applied in successive layers for a total weight of 8.10 kg of paraffin previously melted and diluted to a 40% concentration with methylene chloride at a temperature of 30-45°C.

The methacrylic acid copolymers (Rohm Pharma, Eudragit E and RS type) were applied in acetonic solution. The end amounts were as follows: Eudragit RS kg 0.60; Eudragit E kg 0.30.

During the application of the successive layers 4.80 kg of talc were added.

The release test, carried out according to USP

XXI, Apparatus No. 1, at 100 rpm and with 900 ml of juice of pH 1.2 for the first hour and of 7.5 for the fourth and eighth hour, gave the following results: 1st hour = 13.3%; 4th hour = 47.2%; 8th hour = 82.8%.

After administration of a capsule containing 160 mg of propranolol HCl, the in vivo results showed a pharmacologically active blood level for 24 hours as the known product Inderal LA available in Switzerland, England, etc. With the above formulation, capsules containing from 40 to 250 mg of propranolol HCl may be prepared.

Example 5

Operating as described in Example 4 but with the following per cent composition on dried microgranules

diltiazem HCl	43.6%
neutral granules	22.5% (size 0.7-1 mm)
paraffin (USP XXI, page 1584)	13.0%
Polyvinylpyrrolidone (USP XXI, page 1584)	8.8%
Eudragit E (Rohm Pharma)	2.1%
Eudragit RS (Rohm Pharma)	0.8%
talc	9.2%

the analysis, performed according to USP XXI, Apparatus No. 1, at 100 rpm and in 800 ml of HCl N/10, provided the results reported in Table 2, curve D. The other curves were obtained by increasing or decreasing the membrane amount in comparison with that indicated above. These different release rates were guaranteed by a very good reproducibility. With the above indicated formulation, capsules containing from 50 to 250 mg of diltiazem can be obtained.

Example 6

69.30 kg of neutral microgranules (granular size 0.9 -1.1 mm) were placed in a stainless steel pan and 23.00 kg of isosorbide-5-mononitrate were applied after dissolution in 20.00 kg of acetone and 45.00 kg of methylene chloride in which 0.95 kg of ethylcellulose (ethoxy groups 44.5 - 50.0%) were dissolved.

After drying, the membrane was applied from ethanolic solution. The dried microgranules contained 6.05 kg of ethylcellulose, 0.655 kg of stearic acid (NF XVI, page 1611) and 85 g of talc. The analysis according to USP XXI, Apparatus No. 2, at 100 rpm and with 1000 ml of juice of pH 7.5, provided the following release results:

1st hour = 29.7%
4th hour = 70.4%
8th hour = 88.7%

The studies on 8 volunteers with 50 mg capsules, in comparison with the known product Elantan Long, available in Germany, showed a very good bioequivalence with a posology of one daily capsule.

With the above formulation, capsules containing from 20 to 120 mg of isosorbide-5-mononitrate may be prepared.

Example 7

Operating as described in Example 6, but with the following per cent composition:

phenylpropanoelamine HCl	31.6%
neutral granules	56.5% (0.7-1 mm)

polyvinylpyrrolidone	2.0% (k value = 30)
ethylcellulose	7.7% (ethoxy groups 44.5-50%)
stearic acid (NF XVI, page 1611)	0.7%
talc	1.5%

5 the analysis according to USP XXI, Apparatus No. 1, at 100 rpm, with 500 ml of distilled water, gave the following results:

1st hour = 51.8%
2nd hour = 72.2%
4th hour = 96.4%

10 The per cent release was the same as for the known product Dexatrin, available in Switzerland and U.S.A. - With the above described formulation capsules containing from 10 to 150 mg may be prepared.

15

Example 8

On 33.00 kg of neutral microgranules, prepare as described in Example 1, 40.00 kg of diacerheyn were applied using a binding agent comprising a solution containing 10.20 kg of polyethylene glycol 4000 and 40.00 kg of ethanol. After drying, a membrane comprising 42.20 kg of ethanol, 2.20 kg of ethylcellulose (ethoxy groups 44.5 - 50.0%) and 0.500 kg of stearic acid was applied in solution. The test was performed according to USP XXI, Apparatus No. 2, at 100 rpm, with 900 ml of juice of pH 7.5 added with 0.05% (w/w) of Tween 80, and it gave the following results:

1st hour = 47.0%
4th hour = 73.0%
8th hour = 88.0%
12th hour = 94.0%

Example 9

35 93.00 kg of theophylline were placed in a granulator together with a solution containing 3.50 kg of polyvinylpyrrolidone (k value = 30) and 14.00 kg of ethanol. After drying, the granulate was sieved and only the fractions having a granular size of 500 to 800 microns were retained. The other finer and coarser fractions were applied after micronization, in a coating pan, on selected nuclei with a binding solution containing 3.50 kg of polyvinylpyrrolidone (k value = 30) and 28.00 kg of ethanol.

40 After drying, on 10.00 kg of microgranules a solution comprising 0.84 kg of ethylcellulose (44.5-50.0% ethoxy groups) and 84 g of stearic acid in 16.00 kg of ethanol was applied.

45 The release test carried out according to USP XXI, Apparatus No. 1, at 125 rpm, with 900 ml of distilled water, provided the following results:

1st hour = 12.7%
2nd hour = 22.5%
4th hour = 37.6%
55 6th hour = 49.1%
8th hour = 58.2%
12th hour = 71.0%
16th hour = 82.3%

Example 10

On 10.00 kg of microgranules, obtained by granulation as described in Example 9, a solution containing 0.40 kg of hydroxypropylmethylcellulose (50 cps) and 0.40 kg of stearic acid was applied.

60 The release test performed as in Example 9 gave

the following results:

1st hour = 7.6%
 2nd hour = 21.9%
 4th hour = 45.5%
 6th hour = 61.4%
 8th hour = 72.1%
 12th hour = 86.5%
 16th hour = 93.9%.

Example 11

On 10.00 kg of microgranules, obtained by granulation as described in Example 9, a solution containing 0.35 kg of methacrylic acid copolymer (Eudragit RS) and 0.35 kg of stearic acid in 3.50 kg of acetone and 3.50 kg of ethanol was applied. The release test carried out as in Example 9, provided the following release profile:

1st hour = 24.5%
 2nd hour = 47.1%
 4th hour = 71.5%
 6th hour = 82.1%
 8th hour = 87.8%
 12th hour = 94.0%

Claims

1. A coating membrane for pharmaceutical and industrial purposes, comprising a lipophilic compound alone or in admixture with a hardener component.

2. A coating membrane according to claim 1, characterized in that the lipophilic compound is selected from fatty acids of from 12 to 20 carbon atoms and paraffin, and the hardener component is selected from ethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, methylcellulose, methacrylic acid copolymers, cellulose acetophthalate, polyethylene glycol, polyvinylacetate, polyvinylpyrrolidone, hydroxybutylcellulose, carboxymethylcellulose sodium and polyvinylacetophthalate.

3. A coating membrane according to claim 1, characterized in that the ratio lipophilic compound to hardener component is 0.1% to 100% for the lipophilic compound and 0.9% to 99.9% for the hardener component.

4. A coating membrane according to claim 1, characterized in that the lipophilic compound is applied after its melting.

5. A coating membrane according to claim 1, characterized in that the lipophilic compound and eventually the hardener component are dissolved in organic solvents at a predetermined temperature to give a saturated or 0.1% solution.

6. Pharmaceutical compositions with controlled release of the therapeutically active compound contained therein, characterized by microgranules of an inert material on which a first layer of the therapeutically active compound and thereon a second layer of a lipophilic

substance, alone or in admixture with a hardener component, is applied.

7. Pharmaceutical compositions according to claim 6, characterized in that the therapeutically active compound is selected from ketoprofen, paracetamol, propranolol, diltiazem, isosorbide-5-mononitrate, phenylpropanolamine, diacerheyn, theophylline.

8. Compositions according to claim 6 and 7, characterized in that the lipophilic compound is selected from fatty acids of from 12 to 20 carbon atoms and paraffin, and the hardening agent is selected from ethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, methylcellulose, methacrylic acid copolymers, cellulose acetophthalate, polyethylene glycol, polyvinylacetate, polyvinylpyrrolidone, hydroxybutylcellulose, carboxymethylcellulose sodium and polyvinylacetophthalate.

9. Process for preparing pharmaceutical compositions with controlled release of the therapeutically active compound, characterized in that microgranules of an inert material are coated with a first layer of a therapeutically active compound and then with a second layer consisting of a lipophilic substance alone or in admixture with a hardener component.

10. Process according to claim 9, characterized in that the inert material consists of sucrose and starch, the active ingredient is selected from ketoprofen, paracetamol, propranolol, diltiazem, isosorbide-5-mononitrate, phenylpropanolamine, diacerheyn and theophylline, the lipophilic compound is selected from fatty acids of from 12 to 20 carbon atoms and paraffin, and the hardening agent is selected from cellulose ethers or esters, methacrylic acid copolymers, polyethylene, glycol, polyvinylpyrrolidone, polyvinylacetophthalate and polyvinylacetate.

45

50

55

60

65

0263083

FIG 1

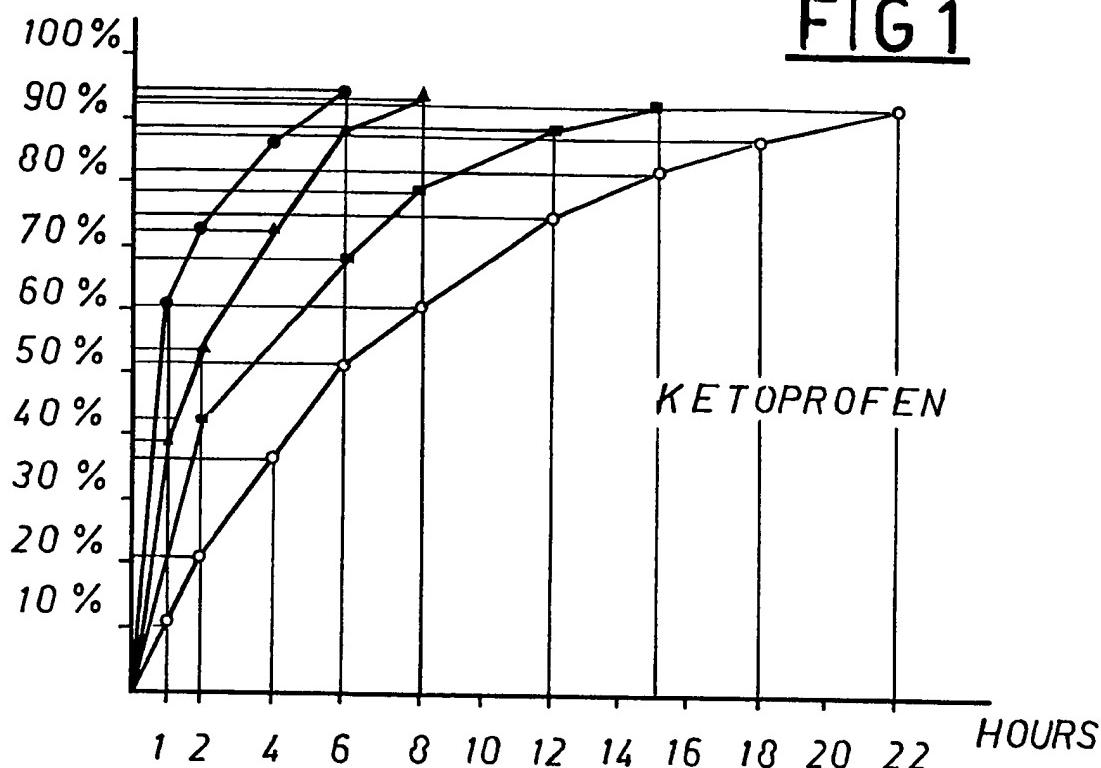
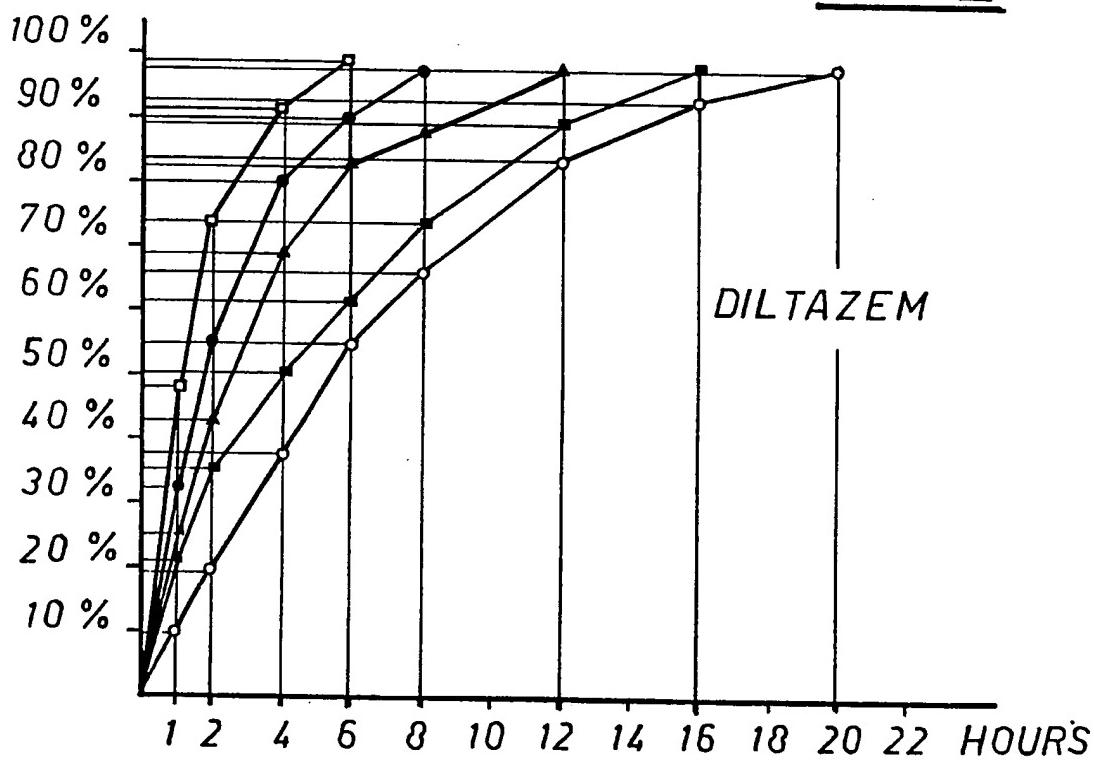


FIG 2





European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 83 0347

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	BE-A- 838 505 (BASF) * Page 6, example 2 - end * ---	1, 2, 4	A 61 K 9/52 A 61 K 9/42
X	GB-A- 595 444 (LLOYD-THOMAS) * Whole document *	1, 2, 4	
X	FR-A-2 237 620 (BYK GULDEN LOMBERG) * Pages 18-20, example 1; pages 24-26, example 6 *	1-3, 5-10	
X	US-A-2 918 411 (HILL) * Whole document *	1-4	
X	DE-C- 939 047 (HOFFMANN-LA ROCHE) * Whole document *	1-3, 5	
X	FR-A-1 329 120 (ABBOTT LABORATORIES) * Page 4, example 3 *	1-3, 5	
X	US-A-4 572 833 (PEDERSEN et al.) * Column 3, line 8 - column 5, line 24; columns 9,10, example 1; claims *	1-6, 9, 10	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
X	GB-A-1 413 186 (TOYO JOZO CO. LTD) * Page 4, example 7; page 5, examples 13-15 *	1-3	A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE	Date of completion of the search 18-12-1987	Examiner BENZ K.F.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

0 273 890
A1

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 87850382.0

(20) Int. Cl.4: A 61 K 9/50
A 61 K 9/08

(22) Date of filing: 07.12.87

(30) Priority: 22.12.86 SE 8605515

(71) Applicant: ASTRA LAKEMEDEL AKTIEBOLAG
S-151 85 Södertälje (SE)

(43) Date of publication of application:
06.07.88 Bulletin 88/27

(72) Inventor: Mattsson, Kjell Johan
Äppelgränd 14
S-151 44 Södertälje (SE)

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

Nicklasson, Alf Gunnar Martin
Bränningestrandsvägen 72
S-151 39 Södertälje (SE)

Sjöqvist, Rolf Ivar
Törnrosavägen 18
S-151 52 Södertälje (SE)

(74) Representative: Danielsson, Sten Ove et al
AB ASTRA Patent and Trademark Department
S-151 85 Södertälje (SE)

(54) A liquid dosage form for oral administration of a pharmaceutically active substance.

(57) A dosage form for oral administration of a pharmaceutically active substance characterized in that it includes a encapsulated or embedded pharmaceutically active substance in a pharmaceutically acceptable non-aqueous liquid.

EP 0 273 890 A1

Description**A liquid dosage form for oral administration of a pharmaceutically active substance****Description**

5

Technical field

The present invention relates to a liquid dosage form for oral administration containing microspheres or microcapsules of a pharmaceutically active substance which substance has either an unpleasant taste or which substance is unstable in aqueous solution or both.

10

The present invention also relates to a method of masking unpleasant taste of a pharmaceutically active substance administered in the form of a solution or suspension and to increase the stability properties of an unstable pharmaceutically active substance administered in the form of a solution or suspension using a non-aqueous liquid carrier.

15

Background of the Invention

Many pharmaceutically active substances have a very unpleasant taste, and they are therefore not suited for oral administration in the form of solutions or suspensions. Because the administration by solutions or suspensions is a very suitable one and in some cases the only oral way feasible, (e.g. when a patient can not accept tablets or capsules) the problem is a serious one. Thus, for administration to children and elderly, oral suspensions or solutions may be advantageous. In the former case, taste is very important in order to have a high patient compliance.

The problem of masking the unpleasant taste of a pharmaceutically active substance in connection with a liquid dosage form for oral administration and where the substance is microencapsulated has been tackled in different ways.

25

In EP 69097 the combination of a microencapsulated active substance with a basic substance prior to preparing a ready to use aqueous suspension is described.

In EP 101418 the combination of a microencapsulated active substance with a high content of sugar prior to preparing a ready to use aqueous suspension is described.

30

The object of the present invention is to provide a ready to use solution or suspension of a pharmaceutically active substance intended to be administered orally wherein the unpleasant taste of the substance has been masked by combining the principles of microencapsulation and a non-aqueous liquid carrier wherein the encapsulated drug is practically insoluble.

Many pharmaceutically active compounds degrade when dissolved in aqueous or hydrophilic solvents. In order to delay this mechanism, preparations have been formulated where the active compound is reconstituted with water prior to use. In many cases, the suspensions or solutions need to be stored in a cold place. A great improvement would therefore be to have a stable formulation from the manufacturer where the active compound is already suspended in a liquid vehicle. However, when it is not possible to make an ready to use suspension, due to physicochemical reasons, the application of microencapsulation or embedding the active compound in a water repellent micro matrix or a sphere can be used in order to increase the solid state stability. Thus, the microspheres or microcapsules can also be mixed with a granulation for reconstitution which creates a more stable system compared to a conventional granulation for reconstitution.

A further object of the invention is therefore to increase the stability of a pharmaceutically active substance which is unstable in aqueous or hydrophilic solution or suspension.

45

A still further object of the invention is to provide controlled release properties of the dosage form according to the invention, thus combining a controlled release with good taste and high stability.

Disclosure of the invention

Aqueous suspensions have been used in all prior attempts to tackle the problem of masking unpleasant taste of a liquid oral formulation using a microencapsulated pharmaceutically active substance.

50

It has now been found that the unpleasant taste of a pharmaceutically active compound intended to be administered orally in the form of a solution or a suspension can be masked if the active compound which must be microencapsulated or embedded in a micromatrix is mixed with a vehicle which consists of a pharmaceutically acceptable non-aqueous liquid, in which the encapsulated drug shows no or extremely low solubility. Hence, it is the combination of a microencapsulated drug and the application of a non-aqueous liquid carrier which makes this particular invention unique.

The present invention provides an improved liquid delivery system for active compounds which have an unpleasant taste. It is also advantageous compared to conventional suspensions or solutions since it prevents the active compound from degrading in the liquid medium. The mechanism behind this phenomenon is first the application of a liquid carrier in which the active compound is not soluble or soluble to a very low extent and

60

secondly the fact that the active compound is microencapsulated or embedded in a micromatrix system. Since the active compound is embedded in a micromatrix structure or is microencapsulated the risk for obtaining an unpleasant taste in the mouth due to dilution or washing of the non-aqueous liquid is reduced due to a delayed release of the active compound from the matrices or microcapsules in aqueous media. The combination of

these two factors is a solid ground for obtaining the above mentioned properties. However, as mentioned above, the application of micromatrices or microcapsules may also be advantageous for a granulation for aqueous reconstitution in terms of solid state stability before reconstitution.

By replacing the aqueous vehicle with a non-aqueous vehicle and by microencapsulating or embedding the active compound in a matrix sphere the following advantages are obtained:

- The active substance can be prepared in a liquid formulation which is ready to use.

These types of formulations are otherwise normally delivered as a dry powder which has to be mixed with water prior to use. Such a product has relatively bad keeping qualities. Besides, this operation is costly in countries where the pharmacies fulfill them. In countries where the patient himself has to add water the risk of mistakes could not be disregarded. In a manufacturing point of view it is often advantageous to handle a liquid product instead of a dry powder and thus avoiding problems in connection with the production environment.

- The formulation of a microencapsulated active substance in a non-aqueous vehicle not only provides masking of an unpleasant taste but affords also enhanced stability. This property is particularly valuable in connection with compounds normally unstable in liquid vehicles, for instance penicillins.

- Furthermore the formulation according to the invention affords controlled release properties to the formulation.

All those pharmaceutically active substances which have an unpleasant taste or which are unstable in solution are well suited for use in connection with this invention. Examples of such active substances are

Chemoterapeutics

bacampicillin, ampicillin, flucloxacillin, tetracycline, dicloxacillin, chloramphenicol, gentamicin, erythromycin, lincomycin, rifampicin, sulphadiazine, sulphamethoxypyridazine, griseofulvina, nitrofurantoina, penicillin V, penicillin G, cephalosporin derivatives.

Adrenergic and betareceptor-stimulators
ephedrine, terbutaline, theophylline, enprophylline

Expectorants and cough depressants

Ethylmorphine, dextromethorphan, noscapine, bromhexine

Heart glucosides and antiarythmics

Digitoxine, digoxin, dispyramide, procainide, tocainide, alprenolol, atenolol, metoprolol pindolol, propranolol

Blood pressure depressants

betanidine, clonidine, guanetidine, methyldopa, reserpine, trimetaphane, hydralazine, bendrophlumetiazide, furosemide, chlorotiazide

Antihistamines

brompheniramine, chlorcyclizine, chlorpheniramine, diphenhydramine, prometazine

Peroral antidiabetics

carbutamide, chlorpropamide, tolazamide, tolbutamide

Sedatives Hypnotics Antidepressants Antipsychotics

meprobamate, chlordiazepoxide, diazepam, buspirone, flunitrazepam, nitrazepam, oxazepam, chloromethiazol, chlorpromazine, fluphenazine, perphenazine prochloroperazine, haloperidol, lithium, alaproclate, zimeldine, amitriptyline, imipramine, nortriptyline, remoxipride, raclopride

Antiepileptics

phenytoine, ethotoin, ethosuximide, carbamazepine

Analgetics Anesthetics

cocaine, morphine, pentazocine, petidine, dextropropoxyphene, methadone, acetylsalicylic acid, diflunisal, phenazone, phenylbutazon, acetaminophene, indometazine, naproxen, piroxicam, lidocaine, etidocaine

Others

cimetidine, quinidine, dicoumarine, warfarine, potassium chloride, chloroquine

Preferred active substances are remoxipride, raclopride, penicillins, cephalosporins, alaproclate, buspirone, diazepam and other benzodiazepins.

Particularly preferred compounds are remoxipride, acetaminophen, phenoxyethylpenicillin, bacampicillin, bensylpenicillin, flucloxacillin and cephalosporin derivatives.

The active substances mentioned above are used in neutral or salt form.

Any salts of the active substances mentioned above can be used, for instance

5

10

15

20

25

30

35

40

45

50

55

60

65

Acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malte, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulphate, tannate, tartrate, teoclate, triethiodide.

Also the further cationic salts can be used. Suitable cationic salts include the alkali metal, e.g. sodium and potassium, and ammonium salts and salts of amines known in the art to be pharmaceutically acceptable, e.g. glycine, ethylene diamine, choline, diethanolamine, triethanolamine, octadecylamine, diethylamine, triethylamine, 1-amino-2-propanol-2-amino-2-(hydroxymethyl)propane-1,3-diol and 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol.

15 Coating and matrix materials

The formation of microencapsulated and matrix material is well known in the art and does not form any part of the present invention. Any coating material can be used. The type of coating will be chosen depending on whether only taste masking is desired or whether a controlled release function or a combination of both is desired. The choice of coating will in either case be obvious to the man skilled in the art.

20 Coating and matrix material to be used are, for instance

Polymers:

25 Synthetic polymers of polyvinyl type and copolymers thereof, e.g. polyvinylchloride, polyvinylacetate, polyvinylalcohol, polyvinylpyrrolidone.

Polyethylene type, e.g. polyethylene, polystyrene.

30 Polymers of acrylic acid or acrylic acid ester type, e.g. methylmethacrylate or copolymers of acrylic monomers.

35 Biopolymers or modified biopolymers of cellulose, e.g. ethylcellulose, cellulose acetate phthalate, cellulose acetate, hydroxy propyl cellulose, hydropropylmethyl cellulose, methylcellulose, Na-carboxymethyl cellulose.

Shellac

35 Gelatin

40 Fats, oils, higher fatty acids and higher alcohols e.g. aluminum monostearate, cetylalcohol, hydrogenated beef tallow, hydrogenated castor oil, 12-hydroxystearyl alcohol, glyceryl mono- or dipalmitate, glyceryl mono- di-, or tristearate, myristyl alcohol, stearic acid, stearyl alcohol.

Polyethyleneglycols

Waxes e.g. bees wax, carnauba wax, Japan wax, paraffin, synthetic wax, spermaceti.

45 Sugars and sugar alcohols e.g. mannitol, sorbitol, sucrose, xylitol, glucose, maltose.

The microcapsules or micromatrices useful for the present invention can be prepared by any of several acknowledge of microencapsulation processes or microsphere or matrix production processes including pan coating, prilling, extrusion and spheroidization, fluid bed processes, spray drying, spray chilling coacervation and other processes.

Microspheres, microcapsules or matrix beads in the size range of 10-1000 microns are suitable for being suspended in the liquid carrier. Preferably, the size range of 50-150 μm are used since this size range is small enough in order to give a smooth appearance in the mouth which is especially important for pediatric formulations. This size range can easily be obtained by means of e.g. spray chilling or spray drying and these processes are also suitable for generating controlled release microcapsules in the same size range. The size range of 50-150 μm is also preferred because of the low risk of crushing the spheres between the teeth after administration as it might be for larger beads.

Any combinations of the above mentioned polymers, fats and waxes can be used for encapsulation purposes, viz, different polymers can be mixed, a polymer can be mixed with a fat or wax etc.

60 The encapsulation of the drug can be achieved in the form of microcapsules, but the encapsulation is not restricted to the micro size.

Microcapsules

65 Microcapsules are defined as a solid or a liquid core enclosed in a coating. The coating may also be referred to as the wall or shell. Various types of microcapsule structures can be obtained depending on the

manufacturing process, e.g. mononuclear spherical, multinuclear spherical, multinuclear irregular, encapsulated mononuclear capsules, dual-walled microcapsules etc. When no distinct coating and core region can be observed, the analogous terms are microparticles, microspheres, micromatrices or microbeads (c.f. multinuclear microcapsules above). The microcapsules usually have a particle size between 1 and 2000 µm. The preferred size range for this invention is 50-150 µm.

5

The microcapsules referred to in the present invention can thus be designed as micromatrices, overcoated micromatrices or overcoated homogeneous microsphere cores.

Non-aqueous vehicle

Non-aqueous vehicle is a pharmaceutically acceptable non-aqueous liquid such as a pharmaceutically acceptable oil, e.g. hydrogenated coconut oil, such as Miglyol® and Viscoleo®, coconut oil, peanut oil, sesame oil, corn oil.

10

Emulsifying agents

Emulsifying agents (super active agents) to be used are for instance:

15

- bile salts or derivatives thereof
- propyl gallat
- sorbiton fatty acid esters
- polyoxyethylene sorbiton fatty acid esters
- polyoxyethylene sorbitol esters
- polyoxyethylene acids
- polyoxyethylene alcohols
- polyoxyethylene adduct not otherwise classified
- mono and diglycerides
- polyoxyethylene glyceryl fatty acid esters
- fusidic acid derivatives
- sodium lanaryl sulphate

20

25

Preferred embodiments

A preferred embodiment of the present invention is obtained when remoxipride is encapsulated in carnauba wax and mixed with a vehicle consisting of hydrogenated coconut oil.

30

Other preferred embodiments are obtained when phenoxyethyl penicillin, bacampicillin, bensypenicillin, flucloxacillin or acetaminophene are encapsulated in carnauba wax and mixed with a vehicle consisting of hydrogenated coconut oil.

35

Still other preferred embodiments are obtained when the active substance is encapsulated in either carnauba wax and beeswax or in ethyl cellulose, carnauba wax and bees wax and mixed with a vehicle consisting of hydrogenated coconut oil.

40

Still another preferred embodiment is obtained when the active substance is encapsulated in either carnauba wax, bees wax, carnauba wax and bees wax or ethyl cellulose and mixed with a vehicle consisting of hydrogenated coconut oil and a suitable emulsifying agent, e.g. bile salts.

The preparation is preferably made by adding the solid powders (i.e. flavouring agents and sugars) to the fluid component by mixing until a homogenous suspension is obtained. Finally the microcapsules are added and gently mixed. The suspension can then be added to glass or plastic bottles. In some cases, a thickening agent is preferable to prevent a too rapid sedimentation of the suspended particles (e.g. aluminum monostearate, stearic acid, bees wax etc.)

45

Best mode of carrying out the invention

Example 1

Remoxipride substance with a particle size less than 10 µm was suspended in a carnauba wax melt at 100°C. The slurry was spray chilled into microspheres with a diameter between 50 and 125 µm.

50

Remoxipride microspheres consist of:

55

Remoxipride hydrochloride monohydrate	40 %
Carnauba wax	60 %

Composition of an oral suspension:

60

Remoxipride microcapsules	13.5 g
Sodium bicarbonate	0.84 g
Caramel flavour	0.50 g
Sucrose powder	35.50 g
Hydrogenated coconut oil	60.00 g

65

In a beaker the oil was added and the sucrose powder was added in small portions while stirring vigorously. Sodium bicarbonate and the flavouring component were added and finally the remoxipride microcapsules were added. The resulting product was a free flowing suspension with a nice appearance.

5 The taste of this product was judged by 10 people and was compared to an aqueous solution with the same concentration of remoxipride. The people was asked to judge if the product was acceptable from a taste point of view compared to the plain remoxipride solution.

Results:

10

Acceptable

Not acceptable

15

The composition

according to ex 1

10

0

20

Remoxipride aqueous
solution

0

10

25

The invented product was superior to a non taste masked aqueous product. Thus the invented product has a very high degree of taste masking as the plain solution has a very bitter taste, which was the main comment from the test panel for the plain remoxipride solution.

30

Example 2

A suspension according to the present invention, containing remoxipride micromatrices (40 % remoxipride and 60 % wall material) was filled in no. 1 hard gelatin capsules. The capsules were administered to two male beagle dogs, and plasma was collected. As reference a solution of remoxipride was used. The dose of the oil suspension (the invented product) was 215 µmol and the solution was 250 µmol of remoxipride. The plasma concentrations of remoxipride were analyzed with a high pressure liquid chromatography method.

35

The maximum plasma concentration obtained (C_{max}) and the extent of bioavailability (AUC) are shown in the Table.

The C_{max} reflects the highest concentration of the drug. A drug that absorbs rapidly reaches a higher C_{max} -value than if it absorbs slowly. The area under the plasma concentration vs. time curve (AUC) reflects the amount of the drug that has been absorbed during the experimental period.

40

Results:

45

	C_{max} µmol/l	AUC		$\mu\text{mol}\cdot\text{h}/\text{l}$	
		Dog 1	Dog 2		
50					
55	The invented product	10.5	9.4	72	56
60	Remoxipride solution	11.9	11.2	72	58

65

It can easily be seen that the invented product is bioequivalent to a plain solution of remoxipride. As a matter of fact, if corrections are made for the dosing difference the invented product has 9 and 4 percent better bioavailability in the two dogs respectively. Thus, the taste masking efforts have no negative effect upon the

biopharmaceutical properties of the drug.

Example 3

Controlled release microcapsules were prepared by means of spray chilling. The particles consisted of 16 % remoxipride hydrochloride monohydrate and 84 % carnauba wax/bees wax. Particles with a size between 53 and 106 µm were collected and used for further experiments.

The release rate of remoxipride from the microcapsules in water at 37°C is given below:

Percent (%) remoxipride released					10
1h	2h	4h	6h	8h	
56	66	80	86	92	15

The controlled release microcapsules were added to an oil formulation.

Composition:

Remoxipride controlled release microcapsules described above: 8.3 g
Caramel flavour 0.5 g
Peppermint oil 0.5 g
Sucrose powder 41.0 g
Hydrogenated coconut oil 60.0 g

Caramel flavour, peppermint oil and sucrose powder were added to the oil and mixed vigorously. Then the controlled release microcapsules were added and gently mixed. The resulting product has thus controlled release properties and it is also taste masked.

Example 4

Dual-walled controlled release microcapsules were prepared by means of spray drying and spray chilling. The microcapsule core consisted of remoxipride hydrochloride monohydrate and ethyl cellulose. The cores were then overcoated with carnauba wax and bees wax, respectively. Particles with a size between 50 and 150 µm were collected and used for further experiments. The final content of remoxipride hydrochloride monohydrate was found to be 16 %.

The release rate of remoxipride from the microcapsules in water at 37°C is given below:

Percent (%) remoxipride released								35
2h	4h	6h	8h	10h	15h	20h	24h	
30	38	45	53	58	70	76	81	40

The controlled release microcapsules were added to an oil formulation.

Composition:

Dual-walled remoxipride controlled release microcapsules 15.6 g
Caramel flavour 0.5 g
Peppermint oil 0.5 g
Sucrose powder 35.4 g

Hydrogenated coconut oil 60.0 g

Caramel flavour, peppermint oil and sucrose powder was added to the oil and mixed vigorously. Then the controlled release microcapsules were added and gently mixed. The resulting product has controlled release properties and it is also taste masked.

5

Example 5

Phenoxyethyl penicillin -K microcapsules consist of

Phenoxyethyl penicillin -K 40 %

Carnauba wax 60 %

The penicillin powder with a particle size less than 10 µm was suspended in a carnauba wax melt at 105°C. The slurry was spray chilled into microspheres with a diameter between 50 and 125 µm.

Composition of an oral suspension:

Phenoxyethyl penicillin -K

microcapsules 11.6 g

Lemon flavour 0.42 g

Strawberry flavour 0.70 g

Maltool 0.28 g

Sucrose powder 30.4 g

Hydrogenated coconut oil 56.5 g

The taste of this product was judged by seven people and was compared to a phenoxyethyl penicillin -K suspension on the market with the same dosage strength (KÄVEPENIN 50 mg/ml). The table summarizes the taste scores obtained where 0 denotes a very bad taste and 100 denotes a perfect taste.

25

	Subject no.	New suspension	Market suspension
30			
	1	91	80
35	2	92	54
	3	93	79
	4	78	31
40	5	91	74
	6	91	47
45	7	77	82
	X	87.6	63.9

The data demonstrate a much better acceptance for the new type of suspension of phenoxyethyl penicillin -K. Also, the taste profile is more irregular for the market suspension and more uniform for the new one which shows that the new suspension has a much better taste in general.

Example 6

Bacampicillin hydrochloride substance with a particle size less than 10 µm was suspended in a carnauba wax melt at 100°C. The slurry was spray chilled into microcapsules with a diameter between 50 and 125 µm.

55

Bacampicillin hydrochloride microcapsules consist of

Bacampicillin hydrochloride 25 %

Carnauba wax 75 %

60

Composition of an oral suspension

Bacampicillin microcapsules 14.14 g

Strawberry flavour 1.30 g

Lemon flavour 0.69 g

65

Maltool 0.29 g

Sucrose powder 25.08 g
 Hydrogenated coconut oil 58.51 g

Example 7

Bacampicillin hydrochloride substance with a particle size less than 10 µm was suspended in a carnauba wax melt at 100°C. The slurry was spray chilled into microcapsules with a diameter between 50 and 125 µm.

5

Bacampicillin hydrochloride microcapsules consist of
 Bacampicillin hydrochloride 40 %
 Carnauba wax 60 %

10

Composition of an oral suspension

Bacampicillin microcapsules 8.81 g
 Strawberry flavour 1.30 g
 Lemon flavour 0.69 g
 Sucrose powder 20.00 g
 Hydrogenated coconut oil 58.51 g

15

Example 8

Phenoxyethyl penicillin -K substance with a particle size less than 10 µm was suspended in a carnauba wax melt at 100°C. The slurry was spray chilled into microcapsules with a diameter between 50 and 125 µm.

20

Phenoxyethyl penicillin -K microcapsules consist of

Phenoxyethyl penicillin -K 40 %
 Carnauba wax 60 %

25

Composition of an oral suspension

Phenoxyethyl penicillin microcapsules 15.63 g

30

Strawberry flavour 0.35 g
 Lemon flavour 0.15 g
 Sucrose powder 61.91 g
 Hydrogenated coconut oil 70.00 g

35

The stability of this product was investigated during storage at 25°C and 37°C for four months. The table shows the assayed quantity of degradation product (mg penicilloic acid/g suspension).

Storage	Time	25°C	37°C	
	0	0.20 mg/g	0.20 mg/g	40
	4 months	0.45 mg/g	0.60 mg/g	45

50

The result in the table shows that the invented formulation of phenoxyethylpenicillin -K is very stable. An increase of only 0.4 mg/g of penicilloic acid is obtained after 4 months' storage at an accelerated storage condition (37°C). This corresponds only to about 1% in relation to the phenoxyethylpenicillin -K concentration in the suspension.

55

Example 9

Bensylpenicillin -K substance with a particle size less than 10 µm was suspended in a carnauba wax melt at 100°C. The slurry was spray chilled into microcapsules with a diameter between 50 and 125 µm.

60

Bensylpenicillin -K microcapsules consist of

Bensylpenicillin -K 40 %
 Carnauba wax 60 %

Composition of an oral suspension

65

5 Bensylpenicillin -K microcapsules 11.6 g
 Lemon flavour 2.2 g
 Strawberry flavour 2.8 g
 Sucrose powder 41.1 g
 Hydrogenated coconut oil 54.7 g

10 **Example 10**
 Flucloxacillin -Na substance with a particle size less than 10 µm was suspended in a carnauba wax melt at 100°C. The slurry was spray chilled into microcapsules with a diameter between 50 and 125 µm.
 Flucloxacillin -Na microcapsules consist of

15 Flucloxacillin -Na 36 %
 Carnauba wax 64 %

15 Composition of an oral suspension

20 Flucloxacillin -Na microcapsules 6.41 g
 Strawberry flavour 1.32 g
 Lemon flavour 0.70 g
 Maltol 0.26 g
 Sucrose powder 31.95 g
 Hydrogenated coconut oil 59.34 g

25 **Example 11**
 1.0 g of polyisobutylene was dissolved in 200 ml of cyclohexane under stirring and heating up to 80°C. After the polyisobutylene was dissolved 1.0 g of ethylcellulose was dissolved. To the cyclohexane solution 2.0 g of Remoxipride hydrochloride monohydrate powder was suspended. Under stirring and controlled cooling, the resulting coated particles were collected and filtered off. The coated particles, or microcapsules, were washed with cool cyclohexane and then air-dried.

30 Composition:
 Microcapsules described above 2.0 g
 Butterscotch flavour 0.1 g
 Sodiumbicarbonate 0.1 g
 Sucrose powder 3.0 g
 Peanut oil 8.0 g
 The microcapsules, flavour, sodium bicarbonate and sucrose were added to the peanut oil and gently mixed.
 The resulting oral suspension was not tasting any bitterness of remoxipride.

40

Claims

- 45 1. A dosage form for oral administration of a pharmaceutically active substance characterized in that it includes an encapsulated or embedded pharmaceutically active substance in a pharmaceutically acceptable non-aqueous liquid.
 2. A dosage form according to claim 1, characterized in that the non-aqueous liquid is a pharmaceutically acceptable oil.
 3. A dosage form according to claim 1, characterized in that the non-aqueous liquid is hydrogenated coconut oil.
 4. A dosage form according to claim 1, characterized in that the pharmaceutically active substance is encapsulated or embedded in carnauba wax.
 5. A dosage form according to claim 1, characterized in that the pharmaceutically active substance is encapsulated or embedded carnauba wax and bees wax.
 6. A dosage form according to claim 1, characterized in that the pharmaceutically active substance is encapsulated or embedded in ethyl cellulose, carnauba wax and bees wax.
 7. A dosage form according to claim 1, characterized in that the active substance is remoxipride.
 8. A dosage form according to claim 1, characterized in that the active substance is selected from the group consisting of bacampicillin, penicillin V, bensylpenicillin and flucloxacillin.
 9. A process for the preparation of a dosage form for oral administration of a pharmaceutically active substance characterized in that solid adjuvants are added to a non-aqueous liquid and mixed therewith until a homogenous suspension is obtained whereafter the pharmaceutically active substance in microencapsulated or embedded form is added and gently mixed with the suspension.
 65 10. A method of obtaining taste masking/controlled release/improved stability in a liquid oral formulation

0 273 890

of a pharmaceutically active substance characterized in adding the pharmaceutically active substance in microencapsulated or embedded form to a vehicle consisting of a non-aqueous liquid.

5

10

15

20

25

30

35

40

45

50

55

60

65



European Patent
Office

EUROPEAN SEARCH REPORT

Application number
87850382.0

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X, Y	DE-A-3 435 747 (ROTHMAN, AVNER, REHOVOT, IL-) * page 6, lines 14-21, page 9, lines 12-14, page 11, lines 30-35 * & SE-A-8404808-1 ---	1,9,10	A 61 K 9/50 9/08
Y	Chemical Abstracts, Vol. 95 (1981) abstract No 225549X, J. Pharm. Pharmacol., 1981, 33(8), 495-9 (Eng.) * Abstract *	4,5,6	
Y	WO-A-81/00205 (BARR, ARTHUR) * claims 1 and 7 *	1,2	
A	EP-A-101 418 (ASTRA LÄKEMEDEL) ---		
A	EP-A-69 097 (ASTRA LÄKEMEDEL) ---		
X	GB-A-1 380 206 (WILLIAM H. RORER INC) * claims 1, 8, 9 *	1,2,3	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			A 61 K
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
STOCKHOLM	04-03-1988	TANNERFELDT A.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			